Large-Scale Hormone Replacement Therapy and Life Expectancy: Results From an International Comparison Among European and North American Populations

Salvatore Panico, MD, MSc, Rocco Galasso, MD, Egidio Celentano, MD, Anna V. Ciardullo, MD, MSc, Luisa Frova, PhD, Riccardo Capocaccia, DrSci, Maurizio Trevisan, MD, MSc, and Franco Berrino, MD

A B S T R A C T

Objectives. An analysis was performed to determine the risks and benefits of a 10-year hormone replacement therapy regimen that had been applied to all women at 50 years of age in 8 countries.

Methods. Cumulative mortality with and without hormone replacement therapy over 20 years was estimated, with both current and predicted total and disease-specific secular mortality trends and the influence of a generational cohort effect taken into account.

Results. In countries with high ischemic heart disease frequency and predictable relative predominance of ischemic heart disease rates over breast cancer rates for the next 20 years, hormone replacement therapy could result in benefits with regard to overall mortality; this advantage decreases in younger-generation cohorts. In countries in which breast cancer mortality predominates over ischemic heart disease in early postmenopause and in which the predictable trends for both diseases reinforce this condition, a negative effect on overall mortality would be observed. In the United States, the effect of large-scale hormone replacement therapy would change over time.

Conclusions. The long-term effect of hormone replacement therapy on life expectancy of postmenopausal women may vary among countries. (*Am J Public Health.* 2000;90:1397–1402)

Hormone replacement therapy has raised great expectations for the prevention of ischemic heart disease in postmenopausal women.[1–8] The consistency of the protective effect of oral hormone replacement therapy on ischemic heart disease found in observational studies is impressive; the estimated magnitude of the protective effect is such that hormone replacement therapy could be one of the most effective preventive measures for postmenopausal women, if it is applied on a large-scale basis. The potential beneficial effects suggested by observational data and the favorable clinical effects on most menopausal symptoms have promoted popularity for this gynecologic therapy, a "magic bullet" able to restore the aging physiology with special respect to coronary arteries.[9–11]

Important questions remain, however. First, how much observational evidence is confirmed by experimental evidence? The results of large clinical studies on the efficacy and safety of hormone replacement therapy for ischemic heart disease primary prevention will not be available until the first decade of the 21st century. This is the case for the Women's Health Initiative in the United States[12] and the Medical Research Council's Women's International Study of Long Duration Oestrogen After Menopause (WISDOM) in the United Kingdom.

Second, in light of both potential benefits and risks, what is the net balance of large-scale use of hormone replacement therapy on population life expectancy? Of concern is the potential increase in breast cancer frequency[13,14] after regular use of hormone replacement therapy for many years, as recommended for the prevention of cardiovascular disease and osteoporotic fractures.[15,16] Decisions about possible large-scale hormone replacement therapy should be based on its expected future benefits or disadvantages for the women who will progressively become eligible for such treatment. Taking into account mortality trends and their projections for the next decades is therefore crucial.

In this article, we address this issue with a simple age-cohort approach, already used in a similar analysis of Italian data.[17] We evaluated the risks and benefits of large-scale oral hormone replacement therapy use on life expectancy, comparatively, in different world regions. We analyzed to what extent the balance between benefits and risks may depend on the specific patterns of mortality in the different populations over time.

Methods

We performed a risk–benefit analysis of the use of oral hormone replacement therapy in postmenopausal women, focusing on the balance between mortality from ischemic heart disease and mortality from breast cancer.

Mortality projections were estimated with a multiplicative age and cohort model. This model assumes that the various birth cohorts share a common age pattern of death probabilities. The cohort effect moves up or down the age curve of mortality without changing its shape.[18]

Salvatore Panico and Anna V. Ciardullo are with the Dipartimento di Medicina Clinica e Sperimentale, Federico II University, Naples, Italy. Salvatore Panico and Maurizio Trevisan are with the Department of Social and Preventive Medicine, State University of New York at Buffalo. Rocco Galasso is with the Regional Oncological Hospital, Rionero, Vulture (PZ), Italy. Egidio Celentano is with the Epidemiology Unit, National Cancer Institute, Naples, Italy. Luisa Frova is with ISTAT, Rome, Italy. Riccardo Capocaccia is with the Istituto Superiore di Sanità, Rome, Italy. Franco Berrino is with the Division of Epidemiology, National Cancer Institute, Milan, Italy.

Requests for reprints should be sent to Salvatore Panico, MD, MSc, Dipartimento di Medicina Clinica e Sperimentale, Federico II University, Via Pansini, 5-80131 Naples, Italy (e-mail: spanico@unina.it).

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This model has been fitted on the logistic scale to mortality and population data obtained for each country in 5-year age classes and single calendar years from 1970 to 1992, from *WHO Annual Statistics*.[19] The model was applied separately for breast cancer and ischemic heart disease and for each country. Future age-specific mortality rates were then estimated for each birth cohort up to the year 2010. First, a common mortality curve was jointly estimated for all cohorts, and second, the age-specific rates of each cohort were obtained from the common curve and the cohort-specific relative risk was estimated for the period 1970 through 1992. These rates were assumed as reference mortality under non–hormone replacement therapy use.

To simulate the effect of hormone replacement therapy, we assumed that all the women in each country had started taking oral estrogen and progestin replacement therapy at 50 years of age and had continued it for 10 years, as applied in previous risk–benefit analyses.[3,6] We estimated mortality levels achievable under such large-scale treatment by correcting reference mortality rates by the relative risks derived from the available observational studies on incidence.[3–8,13,14,20] The risk estimate largely coincided with risk estimates reported for the American Nurses' Health Study[13] and the Collaborative Study on Hormonal Factors in Breast Cancer.[14] As others had done, we used incidence relative risks because data on the effect of hormone replacement therapy on mortality are sparse and contradictory (see Discussion). No overall risk or benefit was expected in the first 5 years of therapy; the benefit for ischemic heart disease was assumed to be 0.88 after 5 years, 0.75 after 10 to 15 years, and 0.88 after 15 to 20 years after the start of hormone replacement therapy; the risk for breast cancer was 1.2 after 10 years and 1.46 after 15 to 20 years after the start of hormone replacement therapy. A lag of 5 years ahead in mortality risk was applied to incidence risks, because the average survival of patients who eventually die from breast cancer is about 5 years.[21]

Cohort-specific cumulative mortality in the absence of hormone replacement therapy was calculated as the sum of age-specific rates estimated by the model for the considered cohort in the age span 50 to 69 years. Corresponding cumulative mortality in the presence of hormone replacement therapy was estimated in the same way from the corrected age-specific rates. The balance between use and nonuse of hormone replacement therapy was estimated in terms of excess or saved deaths for selected birth cohorts (women born in 1935–1940, 1940–1945, and 1945–1950) and for each considered country. Period-specific cumulative mortality rates—shown in Figures 1 and 2—

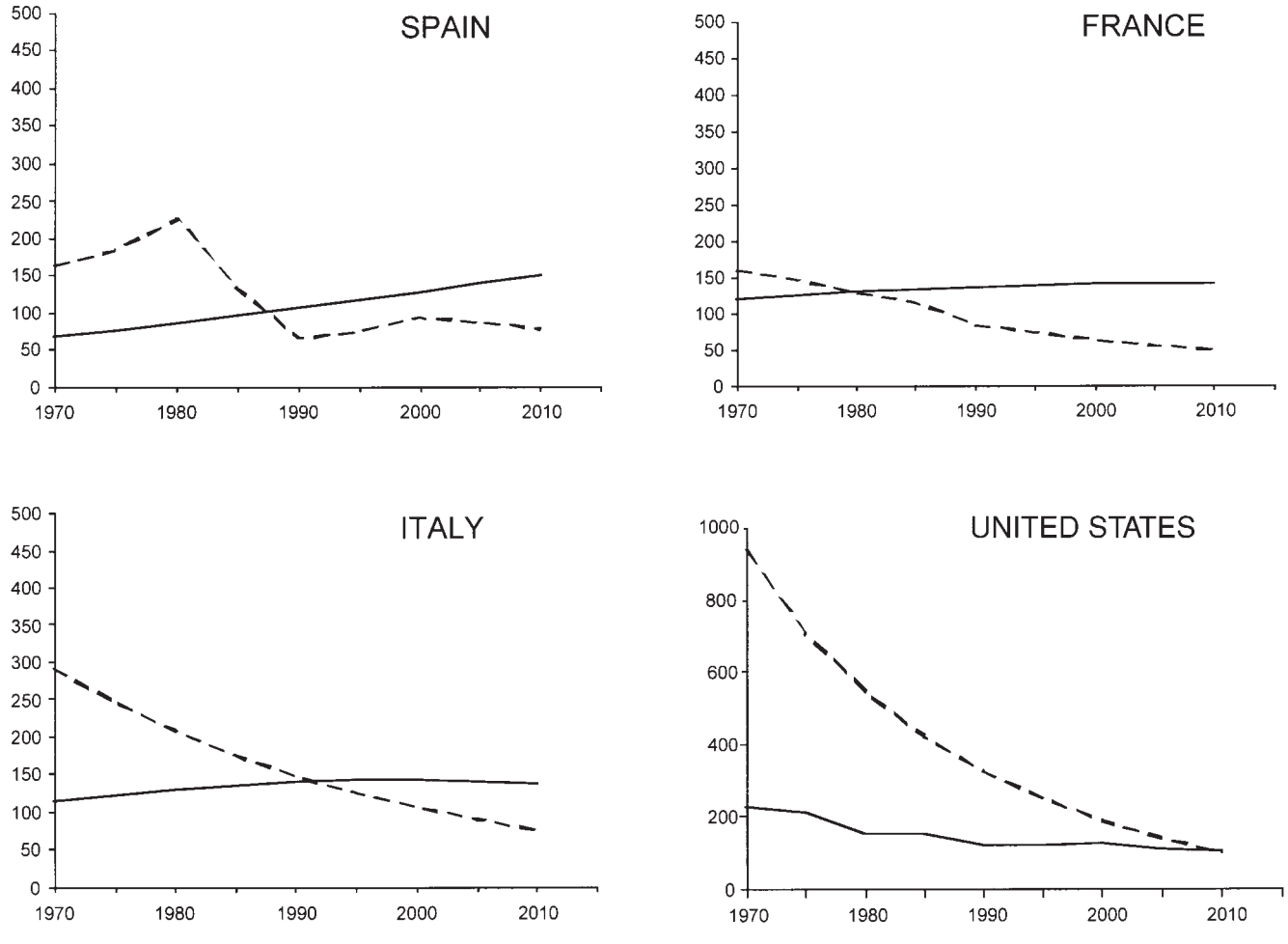

FIGURE 1—Observed (until 1992) and predicted cumulative risks of death from ischemic heart disease (dashed line) and breast cancer (solid line) in the absence of large-scale change in hormone replacement therapy use between ages 50 and 69 per 10 000 women in Spain, France, Italy, and the United States.

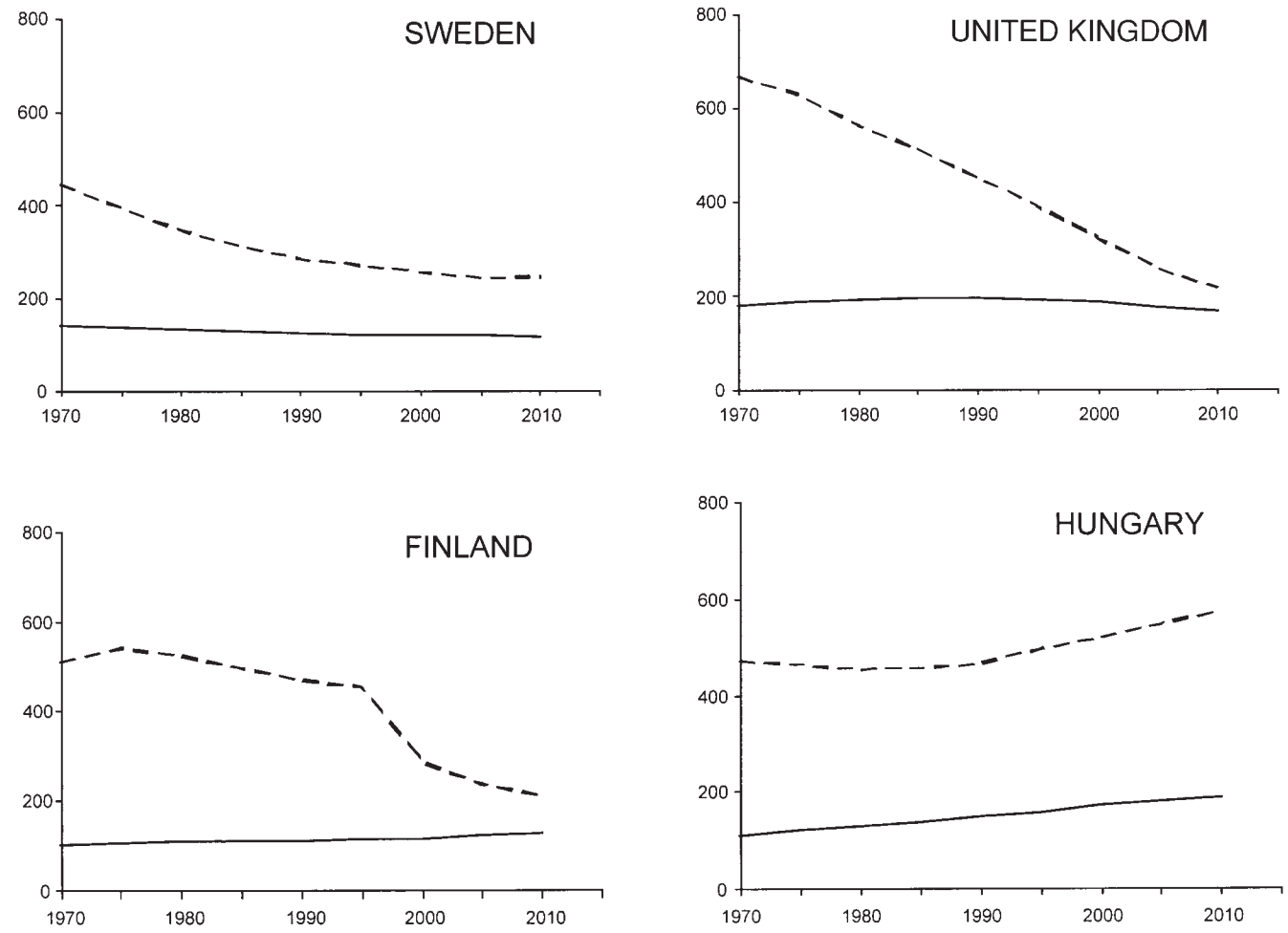

FIGURE 2—Observed (until 1992) and predicted cumulative risks of death from ischemic heart disease (dashed line) and breast cancer (solid line) in the absence of large-scale change in hormone replacement therapy use between ages 50 and 69 per 10 000 women in Sweden, the United Kingdom, Finland, and Hungary.

were estimated as the sum of age-specific rates and by varying birth cohort inversely to age to keep period of death fixed. Cumulative risk of death between 50 and 69 years of age in the year 2000, for instance, is the sum of the mortality rate at 50 years of age for women born in 1950, the mortality rate at 51 years for women born in 1949, and so on up to the mortality rate at 69 years for women born in 1931.

Results

The cumulative risk of death for the different populations shown in Figures 1 and 2 takes into account both period and cohort effects. Observed and predicted cumulative risks of death for ischemic heart disease and breast cancer in women aged 50 to 69 in Spain, France, Italy, and the United States over a period of 40 years (1970–2010) are reported in Figure 1. The first 3 countries are characterized by a low cumulative risk of death for ischemic heart disease and higher breast cancer risk in the 1990s; the trend points to an increasing gap between ischemic heart disease and breast cancer over time. The figure for the United States (bottom right) reflects the dramatic change in ischemic heart disease mortality from 1970 to 2000. The tendency of the curves for ischemic heart disease and breast cancer mortality is to converge, with a possible crossover before the year 2010.

The risks for Sweden, the United Kingdom, Finland, and Hungary are reported in Figure 2. These countries are characterized by higher cumulative mortality risk for ischemic heart disease compared with breast cancer in the 1990s, and the trends over time are such that mortality rates remain higher for ischemic heart disease than for breast cancer; however, for Sweden, the United Kingdom, and Finland, the gap between the 2 curves decreases over time.

Figure 3 summarizes the net effect on overall mortality of estimated excess deaths and saved lives when we applied the estimated relative risks for ischemic heart disease and breast cancer mortality from observational studies to the projected mortality trends over a 20-year period in 3 consecutive age cohorts (women born in 1935–1939, 1940–1944, and 1945–1949). Note that the younger cohort refers to women who may be starting hormone replacement therapy now. As indicated in the Methods section, we simulated a hormone replacement therapy regimen of 10 years starting at 50 years of age.

In Hungary, the United Kingdom, Finland, and Sweden, the expected balance between ischemic heart disease and breast cancer mortality results in a favorable effect of hormone replacement therapy use on all-cause

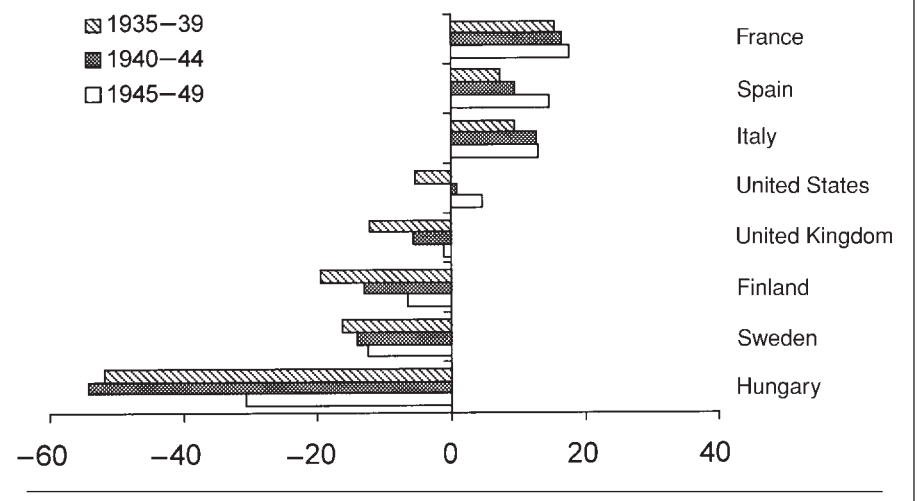

FIGURE 3—Number of predicted excess deaths (right) and saved lives (left) per 10 000 women treated with hormone replacement therapy in subsequent birth cohorts of different countries.

mortality at the end of 20 years of observation (−51.64, −12.24, −19.56, and −16.23, respectively, per 10 000 women in the cohort born in 1935–1939; −54.31, −5.75, −13.12, and −14.10, respectively, in the cohort born in 1940–1944; and −30.77, −1.08, −6.5, and −12.52, respectively, in the cohort born in 1945–1949); however, the advantage tends to decrease over time in younger cohorts. In France, Spain, and Italy, the expected balance indicates an excess number of deaths as a result of hormone replacement therapy (15.57, 7.21, and 9.59, respectively, per 10 000 women in the cohort born in 1935–1939; 16.59, 9.57, and 12.94, respectively, in the cohort born in 1940–1944; and 17.74, 14.70, and 13.02, respectively, in the cohort born in 1945–1949), with an increasing gap between excess and saved deaths over time in younger cohorts.

For the United States, the balance shows small differences between age cohorts, with potential benefits only for the older women and a trend toward a disadvantageous balance in younger cohorts (−5.30 per 10 000 women in the cohort born in 1935–1939, 0.83 in the cohort born in 1940–1944, and 4.56 in the cohort born in 1945–1949).

Discussion

The results of our analysis point out that populations characterized by different patterns of mortality with regard to ischemic heart disease and breast cancer may have a different risk–benefit balance with regard to the effect of hormone replacement therapy on all-cause mortality and life expectancy. In particular, countries that are characterized by a current pattern in which ischemic heart disease is predominant over breast cancer and that will continue to show such a pattern during the first decade after the year 2000 (i.e., Hungary, Finland, United Kingdom, and Sweden) will continue to experience a positive risk–benefit ratio for hormone replacement therapy. However, countries in which breast cancer is predominant over ischemic heart disease and in which the predicted trends indicate a widening of the gap over time (i.e., France, Spain, and Italy) may not experience an overall benefit with regard to life expectancy from large-scale use of hormone replacement therapy. Countries such as the United States, where the current predominance of ischemic heart disease mortality over breast cancer is shifting with time, may experience a decline in overall benefits—up to a negative balance—over time.

These findings suggest that generalized statements with regard to overall benefits of hormone replacement therapy on life expectancy cannot be made and that the overall effect of large-scale use of hormone replacement therapy on mortality will depend on the current pattern of cause-specific mortality in a particular population and its secular trend.

The use of hormone replacement therapy in women entering menopause continues to be a hotly debated issue.[17,22–32] The main reason for the disagreement on the role of hormone replacement therapy in the health of postmenopausal women is the lack of precise detailed information on the potential risks and benefits of hormone replacement therapy from randomized controlled clinical trials. The available evidence from observational studies is strongly suggestive but cannot be used as definitive because of several potentially important biases that may not be excluded from observational studies.

Women taking hormone replacement therapy tend to be more aware of their physical status, to eat better, to be leaner, and to exercise more regularly than those who do not. In one word, they are healthier and more health conscious, and this could contribute to their protection from cardiovascular disease.[22,23,33,34] The available information from observational studies on potential risks and benefits has been used to estimate the effect of large-scale use of hormone replacement therapy on mortality in both the United Kingdom and the United States.[3,6,8] These results suggested an overall benefit of hormone replacement therapy on life expectancy in these 2 countries. However, these studies did not take into account secular trends of mortality for ischemic heart disease and breast cancer in the period for which the estimation was performed, thus missing a crucial piece of information. In addition, the United Kingdom and the United States are countries characterized by a predominance of ischemic heart disease over breast cancer mortality in the early phase of the postmenopausal period (before age 60). These findings therefore cannot necessarily be generalized to countries in which either the predominance of ischemic heart disease over breast cancer is smaller or breast cancer mortality is higher than ischemic heart disease mortality in the early phase of the postmenopausal period.

In some countries, the average age at initiation of hormone replacement therapy is likely to be younger than 50 years. In young women, the ratio between breast cancer and ischemic heart disease is higher than in older women, so early initiation of treatment would increase the risk–benefit ratio.

In our estimates, we did not include mortality due to stroke, endometrial and colon cancer, or osteoporosis and bone fracture. The reasons for these exclusions are as follows:

1. Prospective studies do not indicate a significant protective effect of hormone replacement therapy on stroke mortality or morbidity.[5,7,35]

2. The risks of endometrial hyperplasia and endometrial cancer due to unopposed estrogen appear to be counteracted by the addition of progestins.[20]

3. The average age for hip fracture among postmenopausal women is 80 years; the difference in bone density at 80 years of age between women who used hormone replacement therapy for 10 years has been estimated to be about 3%. Thus, improvement of population mortality rates due to bone fracture is highly improbable among women taking oral hormone replacement therapy for 10 years between 50 and 60 years of age[24]; in addition, it is difficult to estimate the effect of osteoporotic bone fractures on mortality.

4. A negative association of hormone replacement therapy with colon cancer has

been suggested, but findings from studies are inconsistent.[36]

The risks and benefits chosen are based on current estimates and are comparable to those used in other risk–benefit analyses.[3,6,8] We applied a 5-year lag in estimating mortality risk for breast cancer because the average survival of patients who eventually die from breast cancer is about 5 years.[21]

As in previous risk–benefit analyses,[3,6,8] the risk of breast cancer was derived from studies on breast cancer incidence rather than on mortality after hormone replacement therapy. Only a few studies have examined breast cancer mortality after hormone replacement therapy, with inconsistent results.[13,37–40] Willis et al.,[37] for instance, found that ever use of hormone replacement therapy was associated with a 16% decreased risk of fatal breast cancer. This study has been criticized, because women who already had breast cancer were excluded from the analysis at recruitment.[41] The study showed, in particular, that through exclusion of prevalent cases, the risk is underestimated in women who stopped hormone replacement therapy before recruitment. In fact, the women who stopped hormone replacement therapy were included in the analysis if they had not developed breast cancer but were excluded if they had developed cancer. Willis et al. attempted to correct the bias by including the prevalent cases.[41] This is unlikely to be successful, however, because the prevalence of breast cancer—a commonly recognized counterindication for therapy—is expected to be low among women prescribed hormone replacement therapy, as pointed out by Yuen et al.[42]

Colditz et al.,[13] in contrast, found that women who had been using hormone replacement therapy for at least 5 years had a significantly increased risk of breast cancer mortality (odds ratio = 1.45, 95% confidence interval = 1.01, 2.09), which is similar to our assumption. On the other hand, hormone replacement therapy has been found to be associated with improved survival after a diagnosis of breast cancer in some but not all studies[40,43–45]: when stage at diagnosis was controlled for, the apparent survival advantage for prior use of hormone replacement therapy disappeared.[45]

We used mortality as an indicator of potential benefits and risks; therefore, we were unable to consider the potential effect of hormone replacement therapy on other important outcomes, such as psychologic well-being and quality of life. It is important to note that our estimates of potential benefits and risks were based on the available observational information and that, as previously indicated, these estimates may not adequately reflect the real risks and benefits of hormone replacement therapy. A reliable estimate of the overall effect may come from clinical trials. Such evidence is sorely missing and will not be available until the completion of large-scale trials on primary prevention that are being conducted in the United States and Europe. Limited evidence is available from an overview of clinical trials that were not designed to evaluate possible cardiovascular benefits of hormone replacement therapy.[25] Those results have not supported the estimates derived from observational studies and have been heavily criticized.[26–31]

The recently published results of the Heart and Estrogen/Progestin Replacement Study have shown that in women with ischemic heart disease, the overall effect of hormone replacement therapy on future risk of recurrent ischemic heart disease is null.[46] The Heart and Estrogen/Progestin Replacement Study was a secondary prevention trial, whose participants started hormone replacement therapy mostly after the early phase of menopause and were followed up for a short time. These results, however, are not sufficient to falsify the hypothesis that hormone replacement therapy is protective for ischemic heart disease, especially when the treatment is started in the early phase of menopause and when ischemic heart disease has not yet occurred.[32]

Our estimates of the secular trends of mortality are based on current information and therefore may not accurately reflect real trends; however, note that changes in current trends over time are presented only as a potential scenario. The overall message of our findings (i.e., that the relative ranking of ischemic heart disease and breast cancer, both cross-sectionally and longitudinally, is an important determinant of the effect of large-scale use of hormone replacement therapy on life expectancy) should not be affected by changes in these estimates.

In summary, the results of our analyses indicate that populations characterized by different mortality patterns may experience widely different effects of large-scale hormone replacement therapy use after menopause on overall life expectancy. Both public health institutions and physicians are called to acknowledge that this issue is the basis for population-specific guidelines for ischemic heart disease primary prevention in postmenopausal women. Statements with regard to the potential effect of hormone replacement therapy on life expectancy of populations must take into consideration both current and predicted mortality patterns. □

Contributors

S. Panico, R. Galasso, E. Celentano, and A. V. Ciardullo are co-investigators of the Progetto ATENA, an ongoing prospective study on the etiology of chronic disease in women in Italy; they initially proposed the analysis reported in the paper and evaluated the literature and the possible statistical models. L. Frova and R. Capocaccia provided current statistics research in national public institutions and contributed specifically on the use of the original statistical model. M. Trevisan evaluated the US prediction. F. Berrino contributed to the cancer risk section evaluation. All authors participated in several meetings to discuss each part of the paper, and all were involved in conceiving and designing the study, analyzing and interpreting the data, writing the paper, providing critical revisions, and approving the final version of the paper.

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References

1. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease. *JAMA.* 1991;265:1861–1867.
2. Manson JE, Tosteson H, Ridker PM, et al. The primary prevention of myocardial infarction. *N Engl J Med.* 1992;326:1406–1416.
3. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med.* 1992; 117:1016–1037.
4. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med.* 1991;20:47–63.
5. Grodstein F, Stampfer MJ, Manson JA, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med.* 1996;335:453–461.
6. Daly E, Roche M, Barlow D, Gray A, McPherson K, Vessey M. HRT: an analysis of benefits, risks and costs. *Br Med Bull.* 1992;48:368–400.
7. Psaty BM, Heckbert SR, Atkins D, Siscovick DS, Koepsell TD, Wahl PW. A review of the association of estrogens and progestin with cardiovascular disease in postmenopausal women. *Arch Intern Med.* 1993;153:1421–1427.
8. Col NF, Eckman MH, Karas RH, et al. Patient-specific decisions about hormone replacement therapy in postmenopausal women. *JAMA.* 1997; 277:1140–1147.
9. Reis SE, Gloth ST, Blumenthal RS, et al. Ethinil estradiol acutely attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. *Circulation.* 1994;89:52–60.
10. Rosano GM, Sarrel PM, Poole-Wilson PA, Collins P. Beneficial effect of oestrogen on exercise-induced myocardial ischaemia in women with coronary artery disease. *Lancet.* 1993;342(8864): 133–136.
11. Collins P, Rosano GM, Sarrel PM, et al. 17 Beta-estradiol attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease. *Circulation.* 1995; 92:24–30.
12. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials.* 1998; 19:61–109.
13. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of

breast cancer in postmenopausal women. *N Engl J Med.* 1995;332:1589–1593.
14. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 without breast cancer [see Commentaries 1997;350: 1042–1043]. *Lancet.* 1997;350:1047–1059.
15. Scheider DL, Barrett-Connor EL, Morton DJ. Timing of postmenopausal estrogen for optimal density: the Rancho Bernardo Study. *JAMA*. 1997;277:543–547.
16. Coronary heart disease: reducing the risk. International Task Force. *Nutr Metab Cardiovasc Dis.* 1998;8:256–257.
17. Panico S, Galasso R, Celentano E, Frova L, Capocaccia R, Berrino F. Use of hormone replacement therapy. Hormone replacement therapy may not always be right choice to prevent cardiovascular disease [letter]. *BMJ.* 1996;313:687.
18. Caselli G, Capocaccia R: Age, period, cohort and early mortality: an analysis of adult mortality in Italy. *Popul Stud.* 1989;43:133–153.
19. World Health Organization. *WHO Annual Statistics*. Geneva, Switzerland: World Health Organization; several years.
20. Grady D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol.* 1995;58:304–313.
21. Capocaccia R, De Angelis A. Estimating the completeness of prevalence based on cancer registry data. *Stat Med.* 1997;16:425–440.
22. Postuma WFM, Westerndorp RG, Vanderbrouke JP. Cardioprotective effect of hormone replacement therapy in postmenopausal women: is the evidence biased? *BMJ.* 1994;308:1268–1269.
23. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol.* 1996;143:971–978.
24. Ettinger B, Grady D. The waning effect of postmenopausal estrogen therapy on osteoporosis. *N Engl J Med.* 1993;329:1192–1193.
25. Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ.* 1997;315:149–153.
26. Singleton S, Bailey K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer. More women are excluded from treatment arm of such trials because of cardiovascular events [letter]. *BMJ.* 1997;315:676.
27. Shah S, Rhodes L. Impact of postmenopausal hormone therapy on cardiovascular events and cancer. Search for studies was limited [letter] [published correction appears in *BMJ.* 1997;315: 817]. *BMJ.* 1997;315:676–677.
28. Seagroatt V. Impact of postmenopausal hormone therapy on cardiovascular events and cancer. Paper's main conclusion is no longer justified when data from all trials are considered [letter]. *BMJ.* 1997;315:677.
29. Sundkvist T. Impact of postmenopausal hormone therapy on cardiovascular events and cancer. Combining thromboembolic events with cardiovascular events does not support odds ratio of 0.7 [letter]. *BMJ.* 1997;315:677.
30. al-Azzawi F, Thompson J, Halligan A. Impact of postmenopausal hormone therapy on cardiovascular events and cancer. Inclusion of one particular study was inappropriate [letter]. *BMJ.* 1997; 315:677–678.
31. Col NF, Wong JB, Pauker SG, Karas R. Impact of postmenopausal hormone therapy on cardiovascular events and cancer. Study's conclusions were incorrect [letter]. *BMJ.* 1997;315:678.
32. Petitti BD. Hormone replacement therapy and heart disease prevention. *JAMA.* 1998;280: 650–652.
33. Goldstein F. Can selection bias explain the cardiovascular benefits of estrogen replacement therapy? *Am J Epidemiol.* 1996;143:979–982.
34. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Health prior to hormone use: reply to Goldstein. *Am J Epidemiol.* 1996;143: 983–984.
35. Pedersen AT, Lidegaard O, Kreiner S, Ottesen B. Hormone replacement therapy and risk of nonfatal stroke. *Lancet.* 1997;350:1277–1283.
36. *Hormonal Contraception and Post-Hormonal Therapy*. Lyons, France: International Agency for Research on Cancer (IARC); 1999. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*; vol 72.
37. Willis DB, Calle EE, Miracle-McMahill HL, Heath CW Jr. Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States. *Cancer Causes Control.* 1996;7: 449–457.
38. Persson I, Yuen J, Bergkvist L, Schairer C. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy—long-term follow-up of a Swedish cohort. *Int J Cancer.* 1996;67:327–332.
39. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med.* 1997;336:1769–1775.
40. Schairer C, Gail M, Byrne C, et al. Estrogen replacement therapy and breast cancer survival in a large screening study. *J Natl Cancer Inst.* 1999; 91:264–270.
41. Berrino F, Panico S. Hormone replacement therapy and early clinical appearance of low grade breast cancer [letter] [see discussion in *Cancer Causes Control.* 1997;8:673]. *Cancer Causes Control.* 1997;8:672.
42. Yuen J, Persson I, Bergkvist L, Hoover R, Schairer C, Adami HO. Hormone replacement therapy and breast cancer mortality in Swedish women: results after adjustment for 'healthy drug-user' effect. *Cancer Causes Control.* 1993;4: 369–374.
43. Magnusson C, Holmberg L, Norden T, Lindgren A, Persson I. Prognostic characteristics in breast cancer after hormone replacement therapy. *Breast Cancer Res Treat.* 1996;38: 325–334.
44. Bergkvist L, Adami HO, Persson I, Bergstrom R, Krusemo UB. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. *Am J Epidemiol.* 1989;130:221–228.
45. Strickland DM, Gambrell RD Jr, Butzin CA, Strickland K. The relationship between breast cancer survival and prior postmenopausal estrogen use. *Obstet Gynecol.* 1992;80:400–404.
46. Hulley S, Grady D, Bush T, et al, for the HERS Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA.* 1998;280:605–613.